

Summary of Product Characteristics

Zentel 400 mg tablets

Zentel 40 mg/mL suspension

Albendazole

Formulation, Strength and Device* (*if appropriate)

Tablets:

Each tablet contains 400 mg of albendazole.

Suspension:

4% suspension (400 mg albendazole per 10mL suspension).

Excipients

It is mandatory for country product information to include both the complete list of excipients for all locally marketed presentations, and any locally imposed excipient warning statements.

Tablets 200 mg (wet granulation only)	Tablets 400 mg (wet granulation only)	Tablets 400 mg (roller-compaction)	Suspension
Lactose	Lactose monohydrate	Lactose	Aluminium magnesium silicate
Maize starch	Maize starch	Microcrystalline cellulose	Carboxymethylcellulo se sodium
Polyvidone	Povidone	Maize starch	Glycerin
Sodium lauryl sulphate	Sodium lauryl sulphate	Croscarmellose sodium	Polysorbate 80
Sodium starch glycollate	Sodium starch glycollate	Povidone K30	Sorbitan monolaureate
Microcrystalline cellulose	Microcrystalline cellulose	Sodium lauryl sulphate	Potassium sorbate
Sodium saccharin	Sunset yellow lake	Sunset yellow lake	Benzoic acid (see Warnings and Precautions)
Magnesium stearate	Sodium saccharin	Sodium saccharin	Sorbic acid
	Magnesium stearate	Magnesium stearate	Silicone antifoam 1510
	Flavourings	Flavourings (Vanila, Orange and Passion Fruit flavours)	Saccharin sodium
			Flavourings (Vanila,

			Orange and Passion Fruit flavours)
Film coating	Film coating		
Methylhydroxypropyl -cellulose 15	Methylhydroxypropyl -cellulose 15		
Methylhydroxypropyl -cellulose 5	Methylhydroxypropyl -cellulose 5		
Propylene glycol.	Propylene glycol.		

CLINICAL INFORMATION

Indications

Albendazole is a benzimidazole carbamate with anthelmintic and antiprotozoal activity against intestinal and tissue parasites.

INTESTINAL INFECTIONS AND CUTANEOUS LARVA MIGRANS

Short duration treatment at low dose.

Albendazole is indicated in the treatment of the following clinical conditions caused by sensitive intestinal helminths/protozoa (*see Pharmacodynamics* for details on sensitive helminths and protozoa):

- enterobiasis
- hook worm disease (ancylostomiasis and necatoriasis)
- hymenolepsiasis
- taeniasis
- strongyloidiasis
- ascariasis
- trichuriasis
- clonorchiasis and opisthorchiasis (*Opisthorchic viverrini* and/or *Clonorchis sinensis* infections)
- cutaneous larva migrans
- giardiasis in children

SYSTEMIC HELMINTH INFECTIONS

Longer durations of treatment at higher doses.

Albendazole is indicated for the treatment of the following systemic helminth infections (*see Pharmacodynamics* for details of sensitive helminth species).

Echinococcosis

Albendazole shows greatest efficacy in the treatment of liver, lung and peritoneal cysts. Experience with bone cysts and those in the heart and central nervous system is limited.

Cystic Echinococcosis (caused by *Echinococcus granulosus*)

Albendazole is used in patients with cystic echinococcosis:

1. where surgical intervention is not feasible
2. prior to surgical intervention
3. post-operatively if pre-operative treatment was too short, if spillage has occurred or if viable material was found at surgery
4. following percutaneous drainage of cysts for diagnostic or therapeutic reasons

Alveolar Echinococcosis (caused by *Echinococcus multilocularis*)

Albendazole is used in patients with alveolar echinococcosis:

1. in inoperable disease, particularly in cases of local or distant metastasis
2. following palliative surgery
3. following radical surgery or liver transplantation

Neurocysticercosis (larval *Taenia solium* infection)

Albendazole is used for the treatment of patients with:

1. single or multiple cystic or granulomatous lesions of the brain parenchyma
2. arachnoidal or intraventricular cysts
3. racemose cysts

Capillariasis (*Capillaria philippinensis* infection)

Gnathostomiasis (caused by *Gnathostoma spinigerum* and related species)

Trichinosis (caused by *Trichinella spiralis* and *T. pseudospiralis*)

Toxocariasis (caused by *Toxocara canis* and other related species)

Dosage and Administration

INTESTINAL INFECTIONS AND CUTANEOUS LARVA MIGRANS

No special procedures, such as fasting or purging, are required.

If the patient is not cured after three weeks, a second course of treatment is indicated.

Some people, particularly young children, may experience difficulties swallowing the tablets whole and should be encouraged to chew the tablets with a little water, alternatively tablets may be crushed.

Infection	Age	Usual Dose	Duration of dose
Enterobiasis	Adults and children over 2 years of age.	400 mg	Single dose.
Hookworm disease (ancylostomiasis and necatoriasis)			
Ascariasis			
Trichuriasis			
Suspected or confirmed strongyloidiasis	Adults and children over 2 years of age.	400 mg	Once daily for 3 consecutive days. †In cases of proven hymenolepsiasis, retreatment in 10 to 21 days is recommended.
Taeniasis			
Hymenolepsiasis†			
Chlonorchiasis	Adults and children over 2 years of age.	400 mg	Twice daily for 3 days.
Opisthorchiasis			
Cutaneous larva migrans	Adults and children over 2 years of age.	400 mg	Once daily for 1 to 3 days.
Giardiasis	Children 2 to 12 years of age only.	400 mg	Once daily for 5 days.

- **Elderly**

Experience in patients 65 years of age or older is limited. Reports indicate that no dosage adjustment is required, however, albendazole should be used with caution in elderly patients with evidence of hepatic dysfunction (*see Hepatic Impairment and Pharmacokinetics*).

- **Renal impairment**

Since renal elimination of albendazole and its primary metabolite, albendazole sulfoxide, is negligible, it is unlikely that clearance of these compounds would be altered in these patients. No dosage adjustment is required, however, patients with evidence of renal impairment should be carefully monitored.

- **Hepatic impairment**

Since albendazole is rapidly metabolised by the liver to the primary pharmacologically active metabolite, albendazole sulfoxide, hepatic impairment would be expected to have significant effects on the pharmacokinetics of albendazole sulfoxide. Patients with abnormal liver function test results (transaminases) prior to commencing albendazole therapy should be carefully monitored.

SYSTEMIC HELMINTH INFECTIONS

Albendazole should be taken with meals (*see Pharmacokinetics*).

There has been limited experience to date with the use of albendazole at high doses in children under 6 years of age; therefore use in children less than 6 years is not recommended.

Some people, particularly young children, may experience difficulties swallowing the tablets whole and should be encouraged to chew the tablets with a little water, alternatively tablets may be crushed.

Dosages are dependent on the parasite involved, the weight of the patient, and the severity of the infection:

Infection	Patient Body Weight	Dose	Duration of Dosage
Cystic Echinococcosis	> 60 kg	800 mg given in two divided doses of 400 mg.	Daily for 28 days. Treatment for 28 days may be repeated after a 14 day period without treatment for a total of three cycles.
	< 60 kg	15 mg/kg, given in two equally divided doses (maximum dose 800 mg/day).	

Infection	Patient Body Weight	Dose	Duration of Dosage
<i>- Inoperable and multiple cysts</i>			Up to three 28 day cycles of albendazole treatment may be given for the treatment of liver, lung and peritoneal cysts. More prolonged treatment may be required for sites such as bone and brain.
<i>- Pre-operative</i>			Two 28 day cycles should be given where possible prior to surgery. Where surgical intervention is necessary before completion of two cycles, albendazole should be given for as long as possible.
<i>-Post-operative -After percutaneous cyst drainage</i>			Where only a short pre-operative course has been given (less than 14 days) and in cases where emergency surgery is required, albendazole should be given post-operatively for two 28 day cycles separated by 14 drug free days. Additionally, where cysts are found to be viable following pre-surgical treatment or where spillage has occurred, a full two cycle course should be given.
Alveolar Echinococcosis	> 60 kg	800 mg, given in two equally divided doses.	Daily for 28 days. Treatment for 28 days may be repeated after a 14 day period without treatment.
	< 60 kg	15 mg/kg given in two equally divided doses (maximum dose 800 mg/day).	Treatment may need to be prolonged for months or years. Continuous treatment at the same dose has been used for periods of up to 20 months.†

Infection	Patient Body Weight	Dose	Duration of Dosage
Neurocysticercosis±	> 60 kg	800 mg, given in two equal divided doses.	Daily for 7 to 30 days, dependent on the response. A second course may be given with a two-week interval between dose regimes.
	< 60 kg	15 mg/kg, given in two equal divided doses (maximum dose 800 mg/day).	
<i>-Parenchymal cysts and granulomas</i>	> 60 kg	800 mg, given in two equal divided doses	Treatment is usually continued for a minimum of 7 days up to 28 days.
	< 60 kg	15 mg/kg, given in two equal divided doses (maximum dose 800 mg/day).	
<i>-Arachnoidal and ventricular cysts</i>	> 60 kg	800 mg, given in two equal divided doses.	Treatment for 28 days is normally necessary in non-parenchymal cysts.
	< 60 kg	15 mg/kg, given in two equal divided doses (maximum dose 800 mg/day).	
<i>-Racemose cysts</i>	> 60 kg	800 mg, given in two equal divided doses.	Treatment is normally required for at least 28 days. This has been given as a continuous treatment, the duration being determined by clinical and radiological response.
	< 60 kg	15 mg/kg, given in two equal divided doses (maximum dose 800 mg/day).	

†Alveolar Echinococcosis: Treatment is normally given in 28 day cycles as for cystic echinococcosis. It may have to be continued for months or even years. Current follow up suggests that survival times are substantially improved following prolonged treatment. Continuous treatment has been shown in a limited number of patients to lead to apparent cure.

±Neurocysticercosis: Patients being treated for neurocysticercosis should receive appropriate steroid and anticonvulsant therapy as required. Oral or intravenous corticosteroids are recommended to prevent cerebral hypertensive episodes during the first week of treatment.

Infection	Dosage for Adults and Children	Duration of Dosage
Capillariasis	400 mg	Daily for 10 days. # Normally only a single course of treatment is required, but further courses may be given if the clinical and parasitological findings remain positive
Gnathostomiasis	400 mg	Daily for 10 to 20 days (# see above).
Trichinosis	400 mg	Twice daily for 5 to 10 days (# see above).
Toxocariasis	400 mg	Twice daily for 5 to 10 days (# see above).

- **Elderly**

As for ‘Intestinal Infections and Cutaneous Larva Migrans’.

- **Renal impairment**

As for ‘Intestinal Infections and Cutaneous Larva Migrans’.

- **Hepatic impairment**

Since albendazole is rapidly metabolised by the liver to the primary pharmacologically active metabolite, albendazole sulfoxide, hepatic impairment would be expected to have significant effects on the pharmacokinetics of albendazole sulfoxide. Patients with abnormal liver function test results (transaminases) prior to commencing albendazole therapy should be carefully evaluated and therapy should be discontinued if liver enzymes are significantly increased or full blood count decreased by a clinically significant level (see Warnings and Precautions and Adverse Reactions).

Contraindications

- Albendazole should not be administered during pregnancy or in women thought to be pregnant.

- Albendazole is contraindicated in patients with a known history of hypersensitivity to albendazole or other constituents of the dose forms.

Warnings and Precautions

Use in Intestinal Infections and Cutaneous Larva Migrans (short duration treatment at lower dose):

In order to avoid administering albendazole during early pregnancy, women of childbearing age should initiate treatment during the first week of menstruation or after a negative pregnancy test.

Treatment with albendazole may uncover pre-existing neurocysticercosis, particularly in areas with high taenosis infection. Patients may experience neurological symptoms e.g. seizures, increased intracranial pressure and focal signs as a result of an inflammatory reaction caused by death of the parasite within the brain. Symptoms may occur soon after treatment, appropriate steroid and anticonvulsant therapy should be started immediately.

Albendazole suspension contains benzoic acid which is a mild irritant to the skin, eyes and mucous membrane. It may increase the risk of jaundice in newborn babies.

Use in Systemic Helminth Infections (longer duration of treatment at higher doses):

Albendazole treatment has been associated with mild to moderate elevations of hepatic enzymes. Hepatic enzymes generally normalise on discontinuation of treatment. Case reports of hepatitis have also been received (see *Adverse Reactions*). Liver function tests should be obtained before the start of each treatment cycle and at least every two weeks during treatment. If hepatic enzymes are significantly increased (greater than twice the upper limit of normal), albendazole should be discontinued. Albendazole treatment may be restarted when hepatic enzymes have returned to normal limits, but patients should be carefully monitored for a recurrence.

Albendazole has been shown to cause bone marrow suppression and therefore blood counts should be performed at the start and every two weeks during each 28 day cycle. Patients with liver disease, including hepatic echinococcosis, appear to be more susceptible to bone marrow suppression leading to pancytopenia, aplastic anaemia, agranulocytosis and leukopenia and therefore warrant closer monitoring of blood counts. Albendazole should be discontinued if clinically significant decreases in blood cell counts occur (see *Dosage and Administration* and *Adverse Reactions*).

In order to avoid administering albendazole during early pregnancy, women of childbearing age should:

- initiate treatment only after a negative pregnancy test. These tests should be repeated at least once before initiating the next cycle.
- be advised to take effective precautions against conception during and within one month of completion of treatment with albendazole for a systemic infection.

Symptoms associated with an inflammatory reaction following death of the parasite may occur in patients receiving albendazole treatment for neurocysticercosis (e.g. seizures, raised intracranial pressure, focal signs). These should be treated with appropriate steroid and anticonvulsant therapy. Oral or intravenous corticosteroids are recommended to prevent cerebral hypertensive episodes during the first week of treatment.

Pre-existing neurocysticercosis may also be uncovered in patients treated with albendazole for other conditions, particularly in areas with high taeniosis infection. Patients may experience neurological symptoms e.g. seizures, increased intracranial pressure and focal signs as a result of an inflammatory reaction caused by death of the parasite within the brain. Symptoms may occur soon after treatment, appropriate steroid and anticonvulsant therapy should be started immediately.

Albendazole suspension contains benzoic acid which is a mild irritant to the skin, eyes and mucous membrane. It may increase the risk of jaundice in newborn babies.

Albendazole tablets contain lactose. Its use is not recommended in patients with galactose intolerance, lapp lactase deficiency or glucose or galactose malabsorption syndrome (rare hereditary diseases).

Albendazole tablets contain an azo coloring agent (E110 Orange yellow S) and may cause allergic reactions.

Interactions

Cimetidine, praziquantel and dexamethasone have been reported to increase the plasma levels of the albendazole metabolite responsible for the systemic efficacy of the product.

Ritonavir, phenytoin, carbamazepine and phenobarbital may have the potential to reduce plasma concentrations of the active metabolite of albendazole; albendazole sulfoxide. The clinical relevance of this is unknown, but may result in decreased efficacy, especially in the treatment of systemic helminth infections. Patients should be monitored for efficacy and may require alternative dose regimens or therapies.

Pregnancy and Lactation

Fertility

No Text.

Pregnancy

Albendazole should not be administered during pregnancy or in women thought to be pregnant (*see Contraindications*).

Lactation

Adequate human and animal data on use during lactation are not available.

Ability to perform tasks that require judgement, motor or cognitive skills

There have been no studies to investigate the effect of albendazole on driving performance or the ability to operate machinery. However, when driving vehicles or operating machinery, it should be taken into account that dizziness has been reported after using albendazole (see Adverse Reactions).

Adverse Reactions

Data from large clinical studies were used to determine the frequency of very common to rare undesirable reactions. The frequencies assigned to all other undesirable reactions (i.e. those occurring at $< 1/1000$) were mainly determined using post-marketing data and refer to a reporting rate rather than a true frequency.

The following convention has been used for the classification of frequency:

Very common	$\geq 1/10$
Common	$\geq 1/100$ to $< 1/10$
Uncommon	$\geq 1/1000$ to $< 1/100$
Rare	$\geq 1/10,000$ to $< 1/1000$
Very rare	$< 1/10,000$

- **Use in intestinal infections and Cutaneous Larva Migrans** (short duration treatment at lower dose):

Immune system disorders

Rare: Hypersensitivity reactions including rash, pruritus and urticaria

Nervous system disorders

Uncommon: Headache and dizziness

Gastrointestinal disorders

Uncommon: Upper gastrointestinal symptoms (e.g. epigastric or abdominal pain, nausea, vomiting) and diarrhoea.

Hepatobiliary disorders

Rare: Elevations of hepatic enzymes

Skin and subcutaneous tissue disorders

Very rare: Erythema multiforme, Stevens-Johnson syndrome

- **Use in systemic helminth infections** (longer duration of treatment at higher doses):

Blood and the lymphatic system disorders

Uncommon: **Leukopenia**

Very rare: Pancytopenia, aplastic anaemia, agranulocytosis

Patients with liver disease, including hepatic echinococcosis, appear to be more susceptible to bone marrow suppression (See *Dosage and Administration* and *Warnings and Precautions*).

Immune system disorders

Uncommon: Hypersensitivity reactions including rash, pruritus and urticaria

Nervous system disorders

Very common: **Headache**

Common: **Dizziness**

Gastrointestinal disorders

Common: Gastrointestinal disturbances (abdominal pain, nausea, vomiting)

Gastrointestinal disturbances have been associated with albendazole when treating patients with echinococcosis.

Hepatobiliary disorders

Very common: Mild to moderate elevations of hepatic enzymes

Uncommon: **Hepatitis**

Skin and subcutaneous tissue disorders

Common: **Reversible alopecia** (thinning of hair, and moderate hair loss)

Very rare: **Erythema multiforme, Stevens-Johnson syndrome**

General disorders and administrative site conditions

Common: **Fever**

Overdosage

Symptoms and Signs

No Text.

Treatment

Further management should be as clinically indicated or as recommended by the national poisons centre, where available.

Clinical Pharmacology

Pharmacodynamics

ATC Code

P02CA03

Mechanism of Action

Albendazole is a benzimidazole carbamate with antiprotozoal and anthelmintic effects against intestinal and tissue parasites. Albendazole exhibits larvicidal, ovicidal and vermifugal activity, and it is thought to exert its anthelmintic effect by inhibiting tubulin polymerisation. This causes the disruption of the helminth metabolism, including energy depletion, which immobilises and then kills the susceptible helminth.

Pharmacodynamic Effects

Intestinal Infections and Cutaneous Larva Migrans

Albendazole is active against intestinal parasites, including:

– **Nematodes**

Ascaris lumbricoides (roundworm)
Trichuris trichiura (whipworm)
Enterobius vermicularis (pinworm/threadworm)
Ancylostoma duodenale (hookworm)
Necator americanus (hookworm)
Strongyloides stercoralis
Hookworms that cause cutaneous larva migrans.

– **Cestodes**

Hymenolepis nana (dwarf tapeworm).
Taenia solium (pork tapeworm).

Taenia saginata (beef tapeworm).

– **Trematodes**

Opisthorchis viverrini and *Clonorchis sinensis*.

– **Protozoa**

Giardia lamblia (*intestinalis* or *duodenalis*).

Systemic Helminth Infections

Albendazole is effective in the treatment of tissue parasites, including cystic echinococcosis and alveolar echinococcosis caused by infestation of *Echinococcus granulosus* and *Echinococcus multilocularis*, respectively. Albendazole is also effective in the treatment of neurocysticercosis caused by larval infestation of *Taenia solium*, capillariasis caused by *Capillaria philippinensis* and gnathostomiasis caused by *Gnathostoma spinigerum* infestation.

Albendazole has been shown (in clinical trials) to eradicate cysts or significantly reduce cyst size in up to 80% of patients with *Echinococcus granulosus* cysts who were treated.

Where cysts have been investigated for viability following treatment with albendazole, 90% have been non-viable in laboratory or animal studies compared to only 10% of untreated cysts.

In the treatment of cysts due to *Echinococcus multilocularis*, a minority of patients were considered to be cured and a majority had an improvement or stabilisation of disease due to albendazole therapy.

Pharmacokinetics

Absorption

In man, albendazole is poorly absorbed (less than 5%) following oral administration.

The systemic pharmacological effect of albendazole is augmented if the dose is administered with a fatty meal, which enhances the absorption by approximately five-fold.

Distribution

Following oral administration of a single dose of 400 mg albendazole, the pharmacologically active metabolite, albendazole sulfoxide, has been reported to achieve plasma concentrations from 1.6 to 6.0 micromol/L when taken with breakfast.

Metabolism

Albendazole rapidly undergoes extensive first-pass metabolism in the liver, and is generally not detected in plasma. Albendazole sulfoxide is the primary metabolite, which is thought to be the active moiety in effectiveness against systemic tissue infections.

Elimination

The plasma half-life of albendazole sulphoxide is 8.5 hours.

Albendazole sulphoxide and its metabolites appear to be principally eliminated in bile, with only a small proportion appearing in the urine. Elimination from cysts has been shown to occur over several weeks following high and prolonged dosing.

Special Patient Populations

- **Elderly**

Although no studies have investigated the effect of age on albendazole sulfoxide pharmacokinetics, data in 26 hydatid cyst patients (up to 79 years) suggest pharmacokinetics similar to those in young healthy subjects. The number of elderly patients treated for either hydatid disease or neurocysticercosis is limited, but no problems associated with an older population have been observed.

- **Renal Impairment**

The pharmacokinetics of albendazole in patients with impaired renal function have not been studied.

- **Hepatic Impairment**

The pharmacokinetics of albendazole in patients with impaired hepatic function have not been studied.

Clinical Studies

No Text.

NON-CLINICAL INFORMATION

Albendazole has been shown to be teratogenic and embryotoxic in rats and rabbits. Albendazole was negative for evidence of mutagenicity or genotoxicity in a panel of *in vitro* (including Ames inactivated and activated) and *in vivo* tests. In long-term toxicity studies conducted in rats and mice at daily doses of up to 30 times the recommended human doses, no treatment-related tumour formation was seen.

PHARMACEUTICAL INFORMATION

Chemical Structure

No Text.

Shelf-Life

Tablets:

5 years at 30°C

Suspensions:

2% Suspension (400 mg/20 mL)

4 years at 25°C

4% Suspension (400 mg/10 mL)

3 years at 25°C

Storage

Suspensions:

Protect from direct sunlight.

Nature and Contents of Container

Tablets:

Blister packs.

Polypropylene containers and cap.

Suspensions:

Glass/plastic bottle with aluminium cap.

Incompatibilities

Not relevant.

Use and Handling

Suspensions:

Shake well before use.

Marketing Authorisation Holder

GlaxoSmithKline Consumer Healthcare South Africa (Pty) Ltd.,

Hawkins Avenue 39, Epping Industria 1,

Cape Town, 7460, South Africa

Manufacturer

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